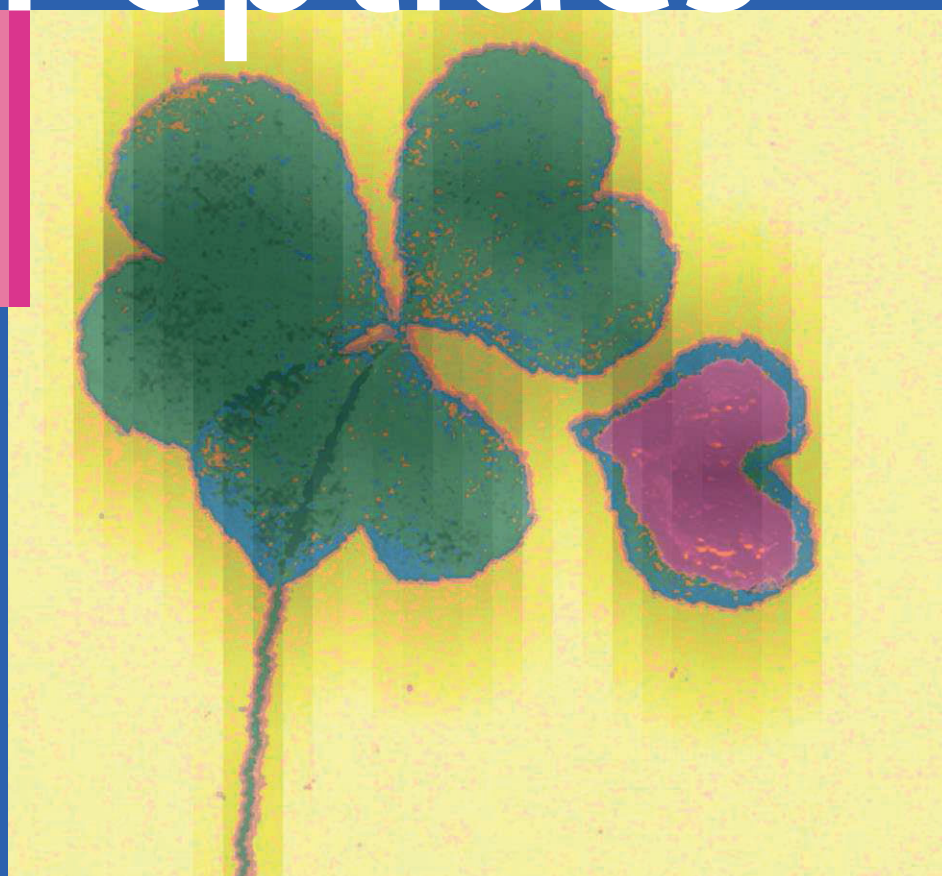


Aldo Clerico
Michele Emdin *Editors*

Natriuretic Peptides



The Hormones of the Heart

 Springer

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Aldo Clerico • Michele Emdin (Eds.)

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The Hormones of the Heart

Foreword by

Luigi Donato

 Springer

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Foreword

Clinical progress is a complex resultant of the interaction between intelligent clinical observation, selected cohort studies, advances in the biophysiological understanding of regulatory mechanisms in health and disease, and technological innovation. In other words, it is through the interplay of clinical, epidemiological, biological and technological research that advances in disease understanding and treatment may be made.

While the above statement represents the philosophy that has inspired the Institute of Clinical Physiology of the Italian National Research Council since its foundation, this book, the work of Aldo Clerico and Michele Emdin, respectively chiefs of laboratory medicine and cardiovascular medicine at the institute, is an excellent demonstrator of the validity of this approach.

The pioneer work of de Bold and a few others would never have emerged from experimental medicine without the fantastic progress in immunometric methods, which has made it possible to move from bench to bedside.

In fact, the current and continuous progress in discovering, understanding and applying the emerging evidence on the endocrine function of the heart, not only represents a Copernican revolution in respect of the traditional mechanical conception, but it unveils entirely new and fascinating perspectives in the treatment and possibly prevention of cardiac failure.

Cardiology is increasingly obliged to enlarge its horizons to the vast regions upstream and downstream of the acute cardiac event. This new demand goes beyond the classical borders of cardiology, and justifies the birth and expansion of cardiology itself into a veritable cardiovascular medicine approach, mastering the multiple regulatory mechanisms and understanding the multiorgan concert coming into play in the long history of the cardiac patient.

Aldo Clerico comes from endocrinology and Michele Emdin from cardiology: they started working together some years ago, and their team was immediately very productive, both at laboratory and bedside level. It is my opinion that with this book they have done a very good job in presenting this complex matter first of all to cardiologists and endocrinologists.

Finally, I want to say that I am deeply convinced that, as far as its clinical relevance is concerned, this field is only at its early dawn.

Luigi Donato

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Contents

About the Authors	XI
Abbreviations	XIII
1 Historical Background and Book Aim	1
Aldo Clerico, Michele Emdin	
1.1 Historical Background	1
1.2 Book Aim and Plan	3
2 The Heart Complexity - The Intrinsic Function (Intrinsic Regulation of Heart Rate and Mechanics)	7
Michele Emdin, Claudio Passino, Fabio Recchia	
2.1 Preamble	7
2.2 Heart Physiology: the Classical View	7
2.3 Neural Control of the Heart: Cardiac Receptors, Afferent/Efferent Neural Pathways, Baro- and Chemoreceptive Feedback.	8
2.3.1 Premises on the Neuro-Humoral Control of the Cardiovascular System	8
2.3.2 Autonomic Control of Heart Rate	9
2.3.3 Afferent Stimuli.	11
2.3.4 Efferent Neural Connections	14
2.3.5 Spinal Cord	15
2.3.6 Medullary Centers	16
2.3.7 Supramedullary Control.	18
2.4 The Integrated Neuro-Hormonal Response: Short- and Long-Term Response.	18
2.5 Heart Physiology: What is New?.	19
3 The Cardiac Natriuretic Hormone System	21
Aldo Clerico, Simona Vittorini	
3.1 Chemical Structure and Gene Evolution of Cardiac Natriuretic Hormones	21
3.2 Genes Encoding for Cardiac Natriuretic Hormones	24
3.3 Regulation of Production/Secretion of ANP and BNP in Cardiac Tissue	28
3.4 Biological Action of CNH	34
3.5 Natriuretic Peptide Receptors and Intracellular Second Messenger Signaling.	39
3.5.1 Genes Encoding for NPRs	39
3.5.2 Biological Function of NPRs	39
3.6 Metabolic Pathways and Circulating Levels of CNH	43
3.6.1 ANP Metabolism	44
3.6.2 BNP Metabolism	44

3.7 CNH System in Fetal Heart and Circulation	46
3.8 CNH Genes and Cardiovascular Diseases	47
3.9 An Integrated Neuro-Hormonal System Regulates Vascular Function	49
3.10 Summary and Conclusion	51
4 Cardiac Natriuretic Hormones as Markers of Cardiovascular Disease: Methodological Aspects	65
Mauro Panteghini, Aldo Clerico	
4.1 General Considerations	65
4.2 Determination of ANP and NT-proANP	67
4.2.1 Competitive Immunoassay Methods for ANP	67
4.2.2 Non-Competitive Immunoassay Methods for ANP	69
4.2.3 Determination of NT-proANP	71
4.3 Determination of BNP and NT-proBNP	71
4.3.1 First-Generation (Manual) BNP Assays	71
4.3.2 Second-Generation (Automated) BNP Assays	72
4.3.3 Determination of NT-proBNP	73
4.3.4 Specificity of BNP/NT-proBNP Assays	74
4.3.5 Quality Specifications for BNP/NT-proBNP Assays	77
4.4 Determination of Other Natriuretic Peptides (CNP, DNP, and Urodilatin)	79
4.5 Summary and Perspectives.	82
5 Clinical Considerations and Applications in Cardiac Diseases	91
Aldo Clerico, Claudio Passino, Michele Emdin	
5.1 Circulating Levels of Cardiac Natriuretic Hormones: Physiological Considerations and Clinical Interpretation.	91
5.1.1 Influence of Age and Gender	91
5.1.2 Comparison between the CNH Assay and that of CNH-Related Pro-Hormone Peptides	94
5.1.3 Resistance to the Biological Action of CNH.	94
5.1.4 Diagnostic Accuracy of CNH Assay in Plasma from Patients with Cardiac Diseases.	99
5.1.5 Biological Variation of Plasma BNP: a Problem or a Clinical Resource?	103
5.2 CNH Assay as Diagnostic and Prognostic Tool in Cardiac Diseases	104
5.2.1 Use of CNH Assay in the Screening and Classification of Patients with Cardiac Dysfunction.	105
5.2.2 Diagnostic Accuracy of CNH Assay in Asymptomatic, Mild Ventricular Systolic Dysfunction	105
5.2.3 Diagnostic Accuracy of CNH Assay in Patients with Suspected HF.	106
5.2.4 Diagnostic Accuracy of CNH Assay in Patients with Acute Myocardial Infarction	108
5.2.5 Diagnostic Accuracy of CNH Assay in Elderly People	108
5.2.6 Detection of Drug Cardiotoxicity by means of BNP Assay.	109
5.2.7 Diagnostic Accuracy of CNH Assay in Coronary Artery Disease	110
5.3 Comparison between the Diagnostic Accuracy of CNH Assay and that of Other Tests and Clinical Investigations	110

5.4 Use of CNH Assay as Prognostic Marker in Cardiovascular Diseases	112
5.4.1 Prognosis in HF	112
5.4.2 Prognosis in ACS	113
5.4.3 Prognostic Relevance of CNH Assay in the General Population	114
5.5 CNH Assay in Management of Patients with HF	114
5.5.1 Clinical Relevance of CNH Assay in Tailoring the Therapy of HF	114
5.5.2 Cost-Effectiveness of CNH Assay in Management of Patients with Acute or Chronic HF.	116
5.6 Summary and Conclusion	117
6 Clinical Applications in Extra-Cardiac Diseases	133
Aldo Clerico, Claudio Passino, Michele Emdin	
6.1 Introduction	133
6.2 Pulmonary Diseases	134
6.3 Kidney Diseases	136
6.4 Acute and Chronic Inflammatory Diseases.	138
6.5 CNH Assay in Cerebrovascular Disease.	139
6.6 Liver Diseases	141
6.7 Thyroid Diseases	141
6.8 Diabetes Mellitus	143
6.9 Obesity.	146
6.10 Adrenal Gland Diseases	147
6.11 Summary and Conclusion	148
7 Cardiac Natriuretic Hormone System as Target for Cardiovascular Therapy.	161
Michele Emdin, Aldo Clerico	
7.1 Background	161
7.2 Effects of Antagonists of Neuro-Hormonal Activation on CNH System	161
7.3 Treatments Targeting the Increase of Circulating Levels of CNH	163
7.3.1 Natriuretic Peptides: Pharmacological Actions	164
7.3.2 Use of Synthetic Natriuretic Peptides: Clinical Trials.	164
7.4 Pharmacological Blockade of Degradation and Receptor Antagonism	167
7.5 Combined ACE and NEP Inhibition	169
7.6 Conclusive Remarks	170
8 “Inconclusive” Remarks: Past, Present and Future of Natriuretic Peptides	177
Subject Index	179

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Abbreviations

ACE, angiotensin-converting enzyme
ACS, acute coronary syndrome
ADH, antidiuretic hormone
AMI, acute myocardial infarction
ANF, atrial natriuretic factor (another term for ANP)
ANP, atrial natriuretic peptide
ANS, autonomic nervous system
AUC, area under the curve
BMI, Body mass index
BNP, brain (B-type) natriuretic peptide
CNH, cardiac natriuretic hormones
CNP, C-type natriuretic peptide
CNS, central nervous system
COPD, chronic obstructive pulmonary disease
COX, cyclooxygenase
CRP, C-reactive protein
CV, coefficient of variation
cTnI, cardiac troponin I
cTnT, cardiac troponin T
DNP, dendroaspis (D-type) natriuretic peptide
ECE, endothelin-converting enzyme
ECG, electrocardiogram
ECLIA, electro-chemi-luminescence-immuno-assay
EDHF, endothelium-derived hyperpolarizing factor
EF, ejection fraction
EIA, enzyme-immuno-assay
ESRD, end-stage renal disease
GATA, zinc-finger proteins binding consensus sequence (A/T)GATA(A/G)
GC, guanylate cyclase
Gi protein, inhibitory guanine nucleotide regulatory (Gi) protein
HF, heart failure
HPLC, high pressure (performance) liquid chromatography
IFCC, International Federation of Clinical Chemistry and Laboratory Medicine
IL, interleukin
IRMA, immuno-radio-metric-assay
KO mice, knockout mice for some genes
LANP, long-acting natriuretic peptide

LDL, low density lipoprotein
LPS, lipopolysaccharide
LVEF, left ventricular ejection fraction
MAP, mean arterial pressure
MHC, myosin heavy chain
NEP, neutral endopeptidase
NO, nitric oxide
NOS, nitric oxide synthase (eNOS, endothelial NOS; iNOS, inducible NOS)
NPPA, human coding gene for ANP
NPPB, human coding gene for BNP
NPV, negative predictive value
NRP, natriuretic receptor peptide
NT-proANP, N-terminal fragment of proANP
NT-proBNP, N-terminal fragment of proBNP
NT-proCNP, N-terminal fragment of proCNP
NTS, nucleus of tractus solitarius
NYHA, New York Heart Association
PCR, polymerase chain reaction
PG, prostaglandin
PGI, prostaglandin I, prostacyclin (PGI₂)
PND, ANP gene
POCT, point-of-care testing
PPV, positive predictive value
ET-1, endothelin 1
PKG, cGMP-dependent protein kinase
PRA, plasma renin activity
RAAS, renin-angiotensin-aldosterone system
RIA, radio-immuno-assay
ROC, receiver operating characteristic
RT PCR, reverse transcription polymerase chain reaction
RVLM, rostral ventrolateral medulla
SAH, subarachnoid hemorrhage
T3, triiodothyronine
T4, tetraiodothyronine, thyroxine
TGF, transforming growth factor
TNF, tumor necrosis factor
VIP, vasoactive intestinal polypeptide
VLM, ventrolateral medulla
VNP, ventricular natriuretic peptide

Historical Background and Book Aim

Aldo Clerico • Michele Emdin

OBERON

*That very time I saw, but thou couldst not,
Flying between the cold moon and the earth,
Cupid all arm'd: a certain aim he took
At a fair vestal throned by the west,
And loosed his love-shaft smartly from his bow,
As it should pierce a hundred thousand hearts...*

A Midsummer Night's Dream
William Shakespeare

1.1 Historical Background

As early as 1976, in the preface to the first edition of his popular monograph on the physiology of the heart, Arnold M. Katz pointed out:

“...Although it remains fashionable to consider the heart as a muscular pump, this organ is much more than a hollow viscus that provides mechanical energy to propel blood through the vasculature. It is an intricate biological machine that contains, within each cell, a complex of control and effector mechanisms...” [1].

Despite this prophetic observation, in the latter part of the past century the dynamics of circulation were stressed and cardiac disease was explained on a purely hemodynamic basis [2]. The discovery by de Bold [3] that the heart also has an endocrine function has made it necessary to revise completely the theoretical framework of heart function. At the dawn of the new century, we should not consider the heart simply as a pump, but rather as a multi-functional and interactive organ, part of a complex network, and an active component of the integrative systems of the body (including nervous, endocrine and immune systems) [4].

The possibility that low-pressure areas of the heart may be able to sense the fullness of the circulation has long intrigued the physiologist. However, the discovery of the cardiac endocrine function was difficult, probably because it contrasted with the general understanding of cardiac function. Indeed, in 1956, Kirsch and colleagues reported the presence of membrane-bound granules in atrial but not ventricular myocytes of guinea pigs [5]. In the same year, Henry and Pearce reported that balloon stretching of the left atrium produced increased urinary flow in dogs [6]. Poche, in 1957, described the same structure as membrane-bound granules, which he called “*dichte Körper*” [7].

In 1959, Bompiani and co-workers [8] reported the presence of “*corps denses*” in rat atrial cardiocytes and in the bundle of His of albino rats, while Jamieson and Palade named these “specific atrial granules” in 1964 [9] (Fig. 1.1).

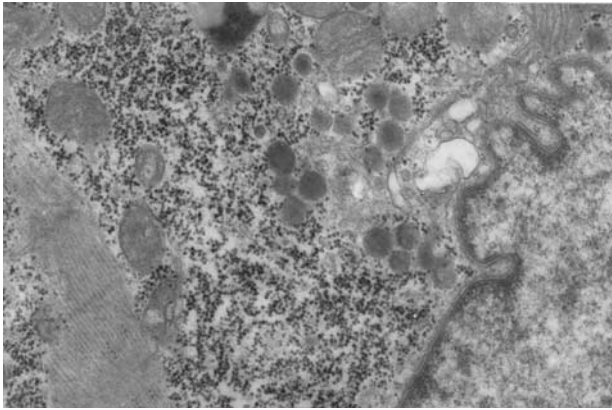


Fig. 1.1. Electron microscopic section through human atrial myocardium, showing atrial cardiomyocytes including some storage granules (i.e., the specific atrial granules containing cardiac natriuretic peptides)

Despite these findings, such a humoral link between atrial and renal sodium excretion received support only in 1976, when Marie et al. [10] reported that atrial granules could be modified by changes in hydro-electrolytic balance. The endocrine function of the heart was definitively established by de Bold et al. [11] in 1981, with the publication of findings regarding the diuretic and natriuretic properties of atrial muscle extracts using the non-diuretic rat bioassay. Injection of such extracts produced a very powerful natriuresis and accompanying diuresis with minimal effect on kaliuresis. The extracts also displayed blood pressure-lowering properties and increased hematocrit. Purification and sequencing of a peptide with the same biological properties as crude atrial extracts resulted in the discovery of a hormone peptide, named atrial natriuretic factor (ANF) by this group of investigators [3, 12].

These seminal studies paved the way for the isolation, purification and identification of a family of natriuretic and vasodilator peptides, now more commonly known as atrial natriuretic peptides (ANP). Furthermore, it was demonstrated that not only atrial but also ventricular cardiomyocytes can secrete peptides with natriuretic activity, in particular the brain natriuretic peptide (BNP), so called because it was first isolated from porcine brain [13].

More recently, C-type natriuretic peptide (CNP) [14], mainly produced and secreted by endothelial cells and by neurons of the central nervous system, and urodilatin [15], produced and secreted by renal cells (and present in urine, but not in plasma), were added to this peptide family. The “C” of CNP follows the fortuitous fact that the names of the first two natriuretic peptides use “A” and “B”, respectively. For this reason, ANP is also called A-type natriuretic peptide and BNP is indicated as B-type natriuretic peptide. Finally, a new peptide, called DNP (dendroaspis natriuretic peptide or

D-type natriuretic peptide) was identified in mammal plasma, but its origin and pathophysiological importance are still unclear [16, 17].

On the other hand, several studies have indicated that natriuretic hormone-like peptides are present in the plant kingdom as well as in the animal kingdom; thus suggesting that this hormonal system, which has been shown to regulate solute transport in vertebrates, has evolved early in evolution [18]. These findings also suggest that natriuretic hormones are necessary for life.

Reliable immunoassays for the measurement of natriuretic peptides in blood and tissues of healthy subjects and patients with cardiovascular disease have been developed [19]. These methods have allowed a more comprehensive understanding of the relevant role played by cardiac natriuretic hormones in physiological conditions and disease [20].

The cultural impact of these studies was of paramount importance. We may consider this as a true “Copernican revolution” in the field of cardiovascular pathophysiology, whose effects can now be directly appreciated also in clinical practice [4, 20]. Cardiac endocrine function should be considered as closely related and integrated with other cardiomyocyte properties, such as excitability and contractility. Moreover, it should be evaluated and measured by means of classical methodological approaches and laboratory techniques commonly used for studying and measuring the activity of endocrine glands. Finally, the results of these investigations should be interpreted in the light of classical endocrinological concepts, such as hormone production, metabolism, peripheral action, and specific receptors [4, 20].

Reductionism, which has dominated biological research for over a century, has provided a wealth of knowledge about individual cellular components and their functions. Despite its enormous success, it is increasingly clear that a discrete biological function can only rarely be attributed to an individual molecule. Instead, most biological characteristics arise from complex interactions between the cell’s numerous constituents, such as proteins, DNA, RNA and small molecules [21, 22]. Therefore, a key challenge for biology in the twenty-first century is to understand the structure and dynamics of the complex intercellular web of interactions that contribute to the structure and function of a living cell.

The behavior of most complex systems, including the biological system, emerges from the orchestrated activity of many components that interact with each other through pair-wise interactions [21]. The components of a biological network can be reduced to a series of nodes that are connected to each other by links, with each link representing the interactions between two components. According to this theory [21], cardiac natriuretic hormones (CNH) should represent highly connected nodes (hubs) in the complex network linking all the regulatory systems of the body (including nervous, endocrine and immune systems) [4].

1.2 Book Aim and Plan

The principal aim of this book is to demonstrate this assumption. It is important to note that this new theory, which considers the heart as a multi-functional and interactive organ that exchanges information with nervous, endocrine and immune systems, is more similar to the popular outlook on the heart. Indeed, some ancient peoples considered the heart as the seat of the soul, and also in modern times the heart is always related to courage, emotion and feeling in popular and artistic imagery.

In Chapter 2 we will summarize the “classical” view of heart physiology; the other chapters will be dedicated to biochemical characteristics and physiological actions (Chap. 3), measurement (Chap. 4), and pathophysiological and clinical relevance, including the cardiac (Chap. 5) and extra-cardiac (Chap. 6) diseases, of the CNH system, respectively. In Chapter 7, we will review the therapeutic applications of natriuretic peptides. Finally, in the last chapter (Chap. 8), we will report our conclusive remarks and also try to take a glance at the years to come.

As each chapter is an independent and self-sufficient unit, we have added a brief introduction at the start and a conclusion at the end of each chapter. For the same reason, the references have been listed at the end of each chapter.

The selection of references was a very serious problem. At the time of writing this manuscript (September 2005), a search for the key words “natriuretic peptides” gave more than 14,000 items, while “atrial natriuretic peptide” more than 13,600 and “B-type natriuretic peptide” more than 3,200 items on the website of the National Library of Medicine (Pub Med, <http://www.ncbi.nlm.nih.gov/>) (Figs. 1.2 and 1.3). It is interesting to note that the time-course seems to be different for articles concerning ANP- or BNP-related peptides. The publications including “atrial natriuretic peptide” seem to have a peak in the 1990s, while the number of articles on BNP and related peptides is still increasing (Fig. 1.3). This effect is clearly due to an explosion of clinical articles and trials concerning the routine use of BNP assays in the diagnosis and risk stratification of patients with cardiovascular diseases in the first years of the new century (see Chap. 5).

It is clearly impossible to cover all articles concerning the CNH; however, taking the reference sections of all the chapters as a whole, we have reported more than 800 references. In order to reduce the number of references, without missing the contribution of some important articles, we usually suggest some authoritative or systematic reviews to readers interested in examining particular topics more closely or in detail. Moreover, for each particular field, we have made every effort to report and discuss the contribution of all the most important scientific groups. We apologize in advance if we have not succeeded in some particular cases.

As demonstrated in Figures 1.2 and 1.3, the studies concerning the CNH (especially BNP) are still growing and expanding. The observations reported in this book are based on the scientific evidence published, judged as the most significant by consensus experts (when available), and should reflect the present knowledge in a topic that is enriched daily by novel methodological, pathophysiological, and clinical progress. This clearly implies a future re-evaluation of some (or even most) of the scientific data.

However, the findings reported in the literature are often conflicting, and consequently there is not a consensus. This is in part expected as a result of species-specific differences (especially between rodents and humans) or of different methods or experimental protocols used. As far as the clinical studies and trials are concerned, the diagnostic accuracy of the CNH assay depends not only on the type of peptide measured (ANP, NT-proANP, BNP or NT-proBNP) and on the respective assaying methods used [19, 20], but also on:

1. The gold (reference) standard used to classify the assay answers (positive/negative, true/false).
2. The clinical condition in which the diagnostic accuracy is tested.
3. The illness prevalence in the examined context.
4. The gravity and severity of the patient’s pathology.
5. The type of statistical analysis or mathematical model used [20, 23].

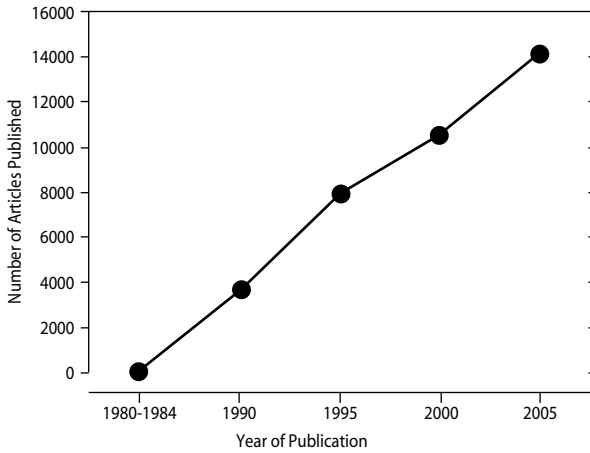


Fig. 1.2. Cumulative number of articles published and covered in the Pub Med website for the words "natriuretic peptides" from 1980 to 20 September 2005. The total number of items was 14,159

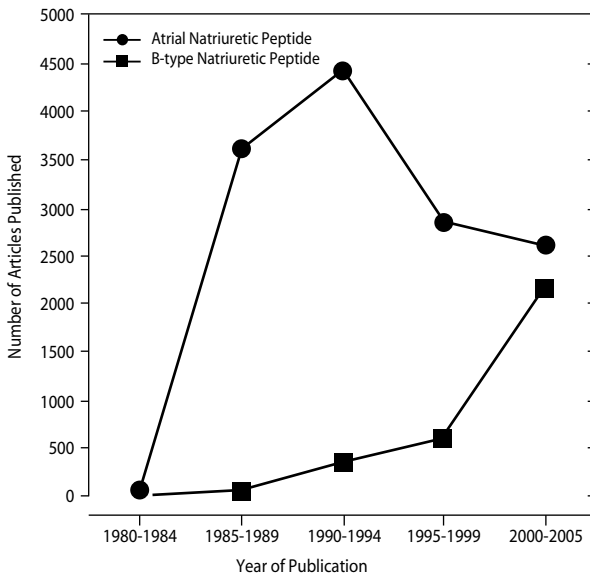


Fig. 1.3. Number of articles published and covered in the Pub Med website for the words "atrial natriuretic peptide" and "B-type natriuretic peptide" from 1980 to 27 September 2005. The articles are grouped in 5-year periods; i.e., each value indicates the total number of articles covered in the 5-year interval. The total number of items was 13,674 for "atrial natriuretic peptide" and 3,220 for "B-type natriuretic peptide", respectively

In the case of conflicting results, we have made every effort to report and discuss all scientific contributions. Of course, some subjective discretionary power is possible in describing the scientific data and, especially, in their discussion and interpretation. We would be glad if the reader could point out to us possible omissions, mistakes or misleading sentences, so that we may improve our work in the future.

This work would not be possible without our Institute: set up in 1968 by Luigi Donato, it is still a unique multidisciplinary environment where clinical care of the patient, at the highest quality level, is accompanied by nearby research facilities. Finally, we would like to thank our co-workers, who in either the clinical setting or the laboratories allow us daily to look for the answer to our curiosity concerning the physiology and pathophysiology of the circulation and cardiovascular diseases.

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The Heart Complexity

The Intrinsic Function (Intrinsic Regulation of Heart Rate and Mechanics)

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*Knowledge is proud that it has learned so much,
wisdom is humble that it knows no more.*

A. Cournand

2.1 Preamble

In classical physiology, the function of the heart is described as the target of autonomic nervous system modulation superimposed on a mechanistic regulation. The aim of this chapter is to remind us of the basic knowledge in this field, as a bridge to the thorough description of the physiological and clinical relevance of the discovery of cardiac endocrine function. An extensive review of the current physiological view of cardiovascular function is beyond the scope of this book and can be found in several excellent textbooks [1, 2].

2.2 Heart Physiology: the Classical View

The heart pumps blood into the pulmonary circulation for the exchange of oxygen and carbon dioxide, and into the systemic circulation to supply tissues with oxygen and nutritive substances, and to convey hormones and other regulatory molecules. The systemic blood flow also contributes to regulation of body temperature.

Respiratory activity is modulated in harmony with cardiovascular function to maintain blood oxygen, carbon dioxide and hydrogen ion concentration within a narrow physiological range.

A healthy heart pumps 3.5 liters of blood per square meter of body surface at rest, at a rate of between 60 and 100 beats per minute. Untrained subjects can increase blood flow up to 12 liters and athletes up to 20 liters during exercise, with the heart rate increasing up to 160 and 190 beats per minute. This shows the great adaptability of cardiac function in response to physiological stimuli.

Cardiac preload corresponds to the volume of blood in the ventricle in the end diastole: in the normal heart an increase in preload enhances the strength of ventricular contraction (Frank-Starling mechanism, or heterometric autoregulation, according to Sarnoff's definition). Cardiac afterload is the resistance against which the ventricle pumps, determined by the combination of aortic impedance and total vascular resistance: normal hearts are able to increase ejected blood volume despite augmented resistance (homeometric autoregulation or Anrep phenomenon). In the presence of a given

preload or afterload, augmented cardiac contractility increases the amount of blood ejected with each beat of the heart (stroke volume).

The cardiac output (equal for the right and left ventricle) and the vascular resistance to blood flow are the main determinant factors in regulating tissue perfusion. The vascular resistances are distributed throughout the vascular bed, occurring mainly at the arterial sites (large arteries 19%, small arteries and arterioles 47%, versus capillaries 27% and veins 7%) and are influenced by the diameter of the precapillary arterioles. Most of the blood volume (64%) resides in the veins (lungs 9%, small arteries and arterioles 9%, large arteries 7%, heart in diastole 7%, capillaries 5%). The systemic circulation is arranged in a parallel fashion and is in series with the pulmonary circulation.

Cardiac rate and contractility, filling volume/pressure and vascular resistances are all influenced by neural control and hormonal agents, acting directly on the heart and vessels and by the regulation of circulating blood volume.

Nevertheless, the heart is not merely a target of a remote control, nor a simple mechanical pump modulated by hydrostatic forces, but because of its anatomy and histology, it holds an intrinsic capability to govern its function by itself. Therefore, the pacemaker cells of the sinoatrial node are able, even when denervated, to maintain the periodical spontaneous depolarization by the inward current of Na^+ ions during phase 4 of the action potential, which is spread through the conduction system and atrial and ventricular cardiomyocytes, forming the basis for electrical and mechanical systole and for the physiological repeat of cardiac cycles.

Moreover, two hearts (right and left) in one serve the two parallel vascular circuits, permitting the coupling of ventilation, blood supply and subsequent gas exchange within the lung, and distribution of oxygenated blood to the periphery of the body. The interventricular septum, simultaneously contributing to the contraction of both ventricles, is the key to this synchronism; its absence independently contributes to the development of heart dysfunction and failure.

The heart has many sensors to provide information about what is going on either within its chambers, concerning intracavitary pressure, or within its wall, with widespread chemo- and mechanoreceptors, evoking local as well as centrally mediated adaptive responses, or providing a painful sensation alerting the individual of pathological events, such as ischemia.

The heart is nourished through the coronary circulation: coronary blood flow varies with aortic pressure, and is influenced by the systolic mechanical compression of intramyocardial vessels, and by metabolic factors released by the myocytes. To adapt to increased metabolic needs, various stimuli, such as hypoxia, increased concentration of hydrogen ions, lactic acid, nitric oxide, carbon dioxide, and particularly adenosine may elicit vasodilatation and an increase in myocardial blood flow.

2.3 Neural Control of the Heart: Cardiac Receptors, Afferent/Efferent Neural Pathways, Baro- and Chemoreceptive Feedback

2.3.1 Premises on the Neuro-Humoral Control of the Cardiovascular System

Circulation is regulated by neural and humoral mechanisms, which, on a beat-to-beat basis, adapt heart rate and contractility, vascular pressures and cardiac output in order to provide an adequate perfusion of brain, myocardium, kidney, lungs and all the other